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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Artcle 36 and Rule 70)

Applicant's or agent's file reference PCT/KR03/00611	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. **PCT/KR2003/000611**	International filing date *(day/month/year)* **27 MARCH 2003 (27.03.2003)**	Priority date *(day/month/year)* 27 MARCH 2002 (27.03.2002)

International Patent Classification (IPC) or national classification and IPC

IPC7 A61L 27/34

Applicant

NOH, Insup et al

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I [X] Basis of the report
   - II [ ] Priority
   - III [ ] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [ ] Certain documents cited
   - VII [X] Certain defects in the international application
   - VIII [ ] Certain observations on the international application

Date of submission of the demamd	Date of completion of this report
07 OCTOBER 2003 (07.10.2003)	20 JULY 2004 (20.07.2004)

Name and mailing address of the IPEA/KR
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International aplication No.
PCT/KR2003/000611

I. Basis of the report

1. With regard to the elements of the international application:*

☐ the international application as originally filed

☒ the description:
pages 1-23 , as originally filed
pages _____ , filed with the demand
pages _____, filed with the letter of _____

☒ the claims:
pages _____ , as originally filed
pages _____ , as amended (together with any statment) under Article 19
pages _____ , filed with the demand
pages 24-28 , filed with the letter of 21/06/2004

☐ the drawings:
pages _____ , as originally filed
pages _____ , filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:
pages _____ , as originally filed
pages _____ , filed with the demand
pages _____, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language English which is

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☒ the language of publication of the international application(under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide** and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained inthe international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disc losure in the international applicationas as filed has been furinshed.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☒ the claims, Nos. 4

☐ the drawings, sheet _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box(Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed." and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION

International aplication No.
PCT/KR2003/000611

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	9-14	YES
	Claims	1-3, 5-8, 15	NO
Inventive step (IS)	Claims	9-14	YES
	Claims	1-3, 5-8, 15	NO
Industrial applicability (IA)	Claims	1-15	YES
	Claims	none	NO

2. Citations and explanations (Rule 70.7)

Reference is made to the following documents from the International Search Report (ISR).
D1: US 6334872
D2: US 4416028
D3: US 5449382

Claim 4 was cancelled in amendments submitted on 21. Jun. 2004. 'claims 1-8' in this report means claims 1-8 but claim 4 hereafter.

The objective of the present invention is to provide a hybrid artificial blood vessel (claims 1-8, 15) and the manufacturing process thereof (claims 9-14) to improve its biocompatibility and patency.

D1 is considered to represent the most relevant state of the art for the subject matter of the present invention with respect to a bioremodelable two- or three- layered tubular prosthesis comprising biodegradable layers and a structural layer. One of the biodegradable layers is the luminal acting as a smooth flow surface and may be treated with drugs for anti-thrombotic effect or other appropriate agents. The structural layer of the prosthesis is made from collagen containing materials.

D2 relates to a blood vessel prosthesis, comprising a non-resolvable tubular support layer and a bio-resolvable inner layer. However, D2 does not teach layers carrying drugs. D3 relates to a bioactivated endoprosthetic device for vessel repair, comprising a stent and a polymer layer formed on the exterior of the stent. Bioactive substances (drugs) are eluted from the microporous structure of the polymer. D3 is however not a tubular object but an invasive stent.

-- Continued in Supplemental Box

International aplication No.
PCT/KR2003/000611

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

Rule 5.1(a)(ii)PCT requires that the description indicate the background art which, as far as known to the applicant, can be regarded as useful for the understanding, searching and examination of the invention, and preferably, cite the documents reflecting such art. It is considered that this rule has not been satisfied in the following reasons: (a) nevertheless D1 & D2 appear to be the most relevant prior arts of the present invention, they have not been mentioned in the international application. (b) it would be appropriate to include a comprehensive discussion of the relevant background art in the present application to differentiate the prior art from the present invention.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of:

Box V

1. Novelty
(a) Regarding claims 1-8:
The subject matter of claim 1 comprises a biodegradable polymer-supporting layer on at least one of an inside and an outside of a non-degradable artificial blood vessel layer, wherein drugs are stored in the microporous space of the non-degradable layer, the biodegradable layer or the interface between the layers.

D1 discloses that the structural layer of the prosthesis may be made from biostable (non-degradable in vivo) polymers such as PTFE in lieu of collagen containing materials (see column 4 lines 32-38). Therefore, the subject matter of D1 is not different in essence from the present invention of claim 1, and D1 is a novelty destroying prior art. Claims 2-8 are dependent on claim 1. The features of claims 2-8 are no more than what is disclosed in D1, and thus the subject matters of claims 2-8 also lack novelty. Accordingly, claims 1-8 of the present invention do not fulfill the criteria set forth in Article 33(2)PCT.

(b) Regarding claims 9-14:
The subject matter of claim 9 is directed to a process preparing for a hybrid artificial blood vessel and differs from prior arts in that micropores of an artificial blood vessel is pretreated with solution B (a biodegradable polymer dissolved in organic solvent) before another biodegradable polymer solution (solution A) that was admixed with porogen(a pore generating agent) is poured onto the mold. Solutions A and B further contain drugs as claimed in claim 12.
Therefore, claim 9 appears to be novel, and its dependent claims 10-14 are considered novel. Accordingly, claims 9-14 fulfill the criteria set forth in Article 33(2) PCT.

(c) Regarding claim 15:
The subject matter of claim 15 relates to an artificial organ prepared by processes of claims 9-14. Description of the present invention does not disclose any other organ but a blood vessel, which is the same object as one of the subject matters of claims 1-8. Therefore, claim 15 does not fulfill the criteria set forth in Article 33(2)PCT.

2. Inventive step
(a) Regarding claims 1-8 & 15:
If novelty should be disputed based on some minor difference of interpretation, it is pointed out that the subject matters of claims 1-8 & 15 would in any case not involve an inventive step (Article 33(3) PCT).

(b) Regarding claims 9-14:
The subject matter of claim 9 is made unique by having an additional step for filling the micropores of the artificial blood vessel with solution B. The step appears to endow the artificial vessel with biocompatibility in addition to the biodegradable layer made from solution A. The filling step seems non-obvious to an ordinary person skilled in the art with respect to enhancing the biocompatibility and patency of the artificial blood vessel made of a non-degradable polymer. Prior arts including D1 and their combination neither indicate nor suggest such step. Therefore, the subject matters of claim 9 and its dependent claims 10-14 are considered to involve inventive step.
Accordingly, the present invention of claims 9-14 meets the criteria set forth in Article 33(3) PCT.

3. Industrial applicability
The present invention is in the field of tissue engineering and intended to provide an artificial blood vessel and the manufacturing process thereof with improved patency and biocompatibility. The invention is thus believed to be industrially applicable. Consequently, claims 1~15 meet the requirements of Article 33(4) PCT.

What is claimed is:

1. A hybrid artificial blood vessel comprising a biodegradable polymer-supporting layer on at least one of an inside and an outside of a non-degradable artificial blood vessel layer.

2. The hybrid artificial blood vessel as claimed in claim 1, wherein the biodegradable polymer comprises at least one polymer selected from the group consisting of synthetic polymers such as polyglicolide, polylactide, poly(lactic-co-glicolic acid) and polycaprolactone, or natural polymers such as chitosan, gelatin, alginic acid, hyaluronic acid and collagen.

3. The hybrid artificial blood vessel as claimed in claim 1, wherein the non-degradable artificial blood vessel layer comprises polyurethane derivatives, DacronR or drawn polytetrafluoroethylene.

4. The hybrid artificial blood vessel as claimed in claim 1, further comprising a drug, which is stored in at least one region selected from the group consisting of the microporous space of the non-degradable artificial blood vessel layer, the biodegradable polymer-supporting layer, and the interface of the artificial blood vessel layer and the supporting layer.

5. The hybrid artificial blood vessel as claimed in claim 4, wherein the drug comprises at least one selected from the group consisting of vascular endothelial growth factor, fibroblast growth factor, nerve growth factor, platelet-derived growth factor, heparin, thrombin, laminin, fibronectin and collagen.

6. The hybrid artificial blood vessel as claimed in claim 1, wherein the biodegradable polymer-supporting layer is porous.

7. The hybrid artificial blood vessel as claimed in

claim 1, wherein the biodegradable polymer-supporting layer is repetitively coated on the artificial blood vessel layer.

8. The hybrid artificial blood vessel as claimed in claim 1, wherein the surface of the non-degradable artificial blood vessel layer is modified physically or chemically.

9. A manufacturing process of a hybrid artificial blood vessel, comprising the steps of:

dissolving biodegradable polymer in organic solvent to prepare biodegradable polymer solution A;

adding porogen to the polymer solution A;

dissolving the same or different biodegradable polymer with the above biodegradable polymer in organic solvent to prepare biodegradable polymer solution B;

incorporating the biodegradable polymer solution B into micropores of an artificial blood vessel layer;

inserting tubes to the inside and outside of the artificial blood vessel layer;

filling the biodegradable polymer solution A in a space between the artificial blood vessel layer and the tubes;

drying the artificial blood vessel layer filled with the biodegradable polymer solution A to remove the organic solvent; and

incubating the artificial blood vessel layer filled with the biodegradable polymer solution A in a water bath to remove the porogen.

10. The manufacturing process as claimed in claim 9, wherein the biodegradable polymer comprises at least one polymer selected from the group consisting of polyglicolide, polylactide, poly(lactic-co-glicolic acid), chitosan, gelatin, alginic acid and collagen.

11. The manufacturing process as claimed in claim 9, wherein the non-degradable artificial blood vessel layer comprises polyurethane derivatives, DacronR or drawn polytetrafluoroethylene.

12. The manufacturing process as claimed in claim 9, wherein the biodegradable polymer solutions A and B further comprise a drug which contains growth factors or extracellular matrices.

13. The manufacturing process as claimed in claim 12, wherein the drug comprises at least a drug selected from the group consisting of vascular endothelial growth factor, fibroblast growth factor, nerve growth factor, platelet-derived growth factor, heparin, thrombin, laminin, fibronectin and collagen.

14. The manufacturing process as claimed in claim 9, wherein the surface of the non-degradable artificial blood vessel layer is modified physically or chemically.

15. An artificial organ for tissue engineering use prepared by any one of manufacturing processes of claims 9 and 14.

INTERNATIONAL SEARCH REPORT

...ternational application No.
PCT/KR03/00611

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 A61L 27/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61L 27/34, A61F 2/00, A61L27/00, A61F2/06

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korea Patent and Applications for Inventions since 1975
Korea Utility Models and Applications for Utility Models since 1975
Japanese Utility Models and application for Utility Models since 1975

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKIPASS, WPI, USPTO, INSPECT"blood, vessel, prosthesis, ePTFE, poly glycolic acid, biodegradable, etc."

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6334872 B1 (Organogenesis Inc.) 01 Jan 2002 -see Figure1B and pages 2-10	1-8
Y	US 5449382 A (Michael P. Dayton) 12 Sep 1995 -see pages 3-5	1-8
Y	US 4416028 A (Ingvar Eriksson et al.) 22 Nov 1983 -see the entire document-	1-3, 6-8
A	US 6197051 B1 (Boston Scientific Corporation), 06 Mar 2001 -see claims-	1-8

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 JULY 2003 (07.07.2003)	08 JULY 2003 (08.07.2003)

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR03/00611

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6334872 B1	01 Jan 2002	WO 95/22301 A1	24 Aug 1995
		EP 746268 A4	01 Apr 1998
		CA 2183056 C	10 Jul 2001
		JP 9509085 T2	16 Sep 1997
US 5449382 A	12 Sep 1995	none	
US 4416028 A	22 Nov 1983	none	
US 6197051 B1	06 Mar 2001	WO 98/57671 A3	15 Apr 1999
		EP 1011739 A2	28 Jun 2000
		JP 12513988 T2	24 Oct 2000

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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International Bureau

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WO 03/080142 A1

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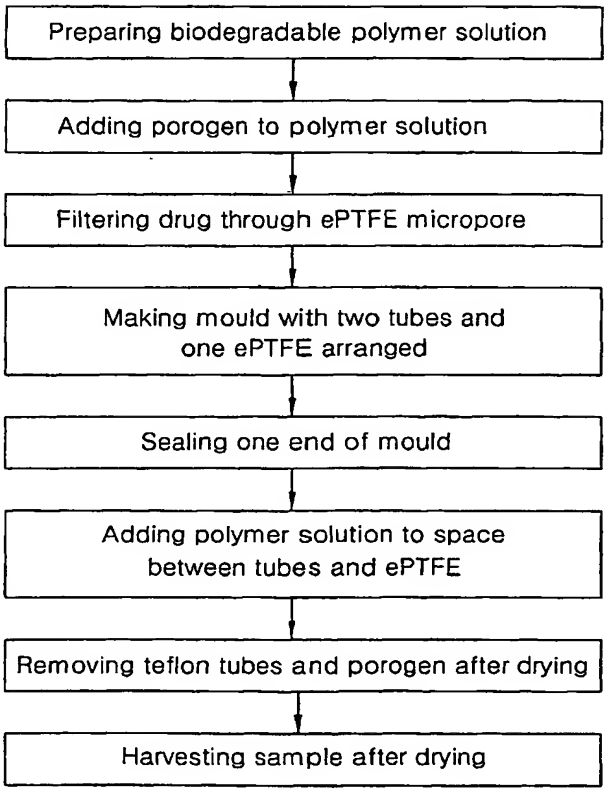
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: HYBRID GRAFTS INCLUDING BIODEGRADABLE POLYMER SUPPORTING LAYER AND MANUFACTURING PROCESS THEREOF



(57) Abstract: The present invention relates to a hybrid artificial blood vessel including a biodegradable polymer supporting layer and the manufacturing process thereof. There is provided a hybrid artificial blood vessel and a manufacturing process thereof, constructing a biodegradable supporting layer on the inner and outer surface of the hybrid artificial blood vessel, thereby increasing biocompatibility and enhancing circulation of blood vessel.

WO 03/080142 A1

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

HYBRID GRAFTS INCLUDING BIODEGRADABLE POLYMER SUPPORTING LAYER AND MANUFACTURING PROCESS THEREOF

Field of the Invention

The present invention relates to a hybrid artificial blood vessel comprising a biodegradable polymer-supporting layer, and more particularly to a hybrid artificial blood vessel and a manufacturing process for the hybrid artificial blood vessel, which comprises a drug and a biodegradable supporting layer on the inner and outer surfaces of the vessel to improve the biocompatiblility and patency of the artificial blood vessel.

Description of the Prior Art

As generally known in the art, artificial blood vessels are artificial organs used for the purpose of repairing the blocked circulation in vivo. Since artificial blood vessels have the characteristic of being permanently implanted in

the body, they are required to have high safety and be composed of materials having good biocompatibility and histocompatibility.

Artificial blood vessels for medical use currently available on the market include those made of PET or drawn polytetrafluoroethylene film (hereinafter, referred to 'ePTFE') and those originating in living tissue. Particularly, the ePTFE is a polymer material used for artificial blood vessels having a microporous structure of a micron unit. The ePTFE having a large diameter having an inner diameter of at least 5 mm is commercially available for transplantation use in patients, but the ePTFE having a small diameter has a difficulty for use as an artificial blood vessel because of low patency after transplant.

Meanwhile, the existing ePTFE processing methods include a plasma treatment and a method inducing cell adhesion on ePTFE surface by coating cell adhesion-inducing proteins on the surface, but the methods have been limited for use in transplantation in patients for a long time because cell cultures are detached from the surface of

artificial blood vessels if transplanted into blood vessels in the body.

Therefore, there is a need for an ePTFE artificial blood vessel for tissue engineering use to improve the biocompatibility and patency of the ePTFE artificial blood vessel.

Summary of the Invention

Accordingly, the present invention has been made to solve the above-mentioned problems occurring in the prior art, and an object of the present invention is to provide a hybrid artificial blood vessel, which includes a biodegradable supporting layer.

It is another object of the present invention to provide a method for manufacturing a hybrid artificial blood vessel, which includes a biodegradable supporting layer.

In order to accomplish the first object, there is provided a hybrid artificial blood vessel comprising biodegradable polymer-supporting layers on at least one of

inner and outer surfaces of non-degradable artificial blood vessels.

In the hybrid artificial blood vessel, the biodegradable polymer is preferably at least one polymer selected from the group consisting of polyglycolide, polylactid, PLGA [Poly(Lactic-co-Glycolic Acid)], chitosan, gelatin, alginic acid and collagen.

In the hybrid artificial blood vessel, the non-degradable artificial blood vessels preferably comprise polyurethane derivatives, DacronR or drawn polytetrafluoroethylene.

According to an embodiment of the present invention, the hybrid artificial blood vessel further contains a drug which is preferably stored in at least one region selected from the microporous space of the non-degradable artificial blood vessel layer, biodegradable polymer-supporting layers, and the interfaces of the artificial blood vessel layers and the supporting layers.

In this embodiment of the present invention, the drug preferably comprises at least one selected from vascular

endothelial growth factor, fibroblast growth factor, nerve growth factor, platelet-derived growth factor, heparin, thrombin, laminin, fibronectin and collagen.

In another embodiment of the present invention, the biodegradable polymer-supporting layer is preferably porous.

In yet another embodiment of the present invention, the biodegradable polymer-supporting layers are preferably formed on the artificial blood vessel layer by repetitive coating.

In yet another embodiment of the present invention, the surfaces of the non-degradable artificial blood vessel layer are preferably modified physically or chemically.

In order to accomplish the second object, there is provided a manufacturing process of a hybrid artificial blood vessel comprising the steps: dissolving biodegradable polymer in organic solvent to prepare biodegradable polymer solution A; adding porogen to the polymer solution A; dissolving the same or different biodegradable polymer with the above biodegradable polymer in organic solvent to prepare biodegradable polymer solution B; incorporating the

biodegradable polymer solution B into the micropores of an artificial blood vessel layer; inserting tubes to the inside and outside of the artificial blood vessel layer; filling the biodegradable polymer solution A in the space between the artificial blood vessel layer and the tubes; drying the artificial blood vessel layer filled with the biodegradable polymer solution A to remove the organic solvent; and incubating the artificial blood vessel layer filled with the biodegradable polymer solution A in a water bath to remove the porogen.

Brief Description of the Drawings

The above and other objects, features and advantages of the present invention will be more apparent from the following detailed description taken in conjunction with the accompanying drawings, in which:

Fig.1 is a scheme for the manufacturing process of a hybrid artificial blood vessel comprising biodegradable polymer-supporting layers according to one embodiment of the

present invention;

Fig.2 is a sectional drawing of a hybrid artificial blood vessel comprising biodegradable polymer-supporting layers according to one embodiment of the present invention;

Fig.3 is a scanning electron micrograph showing a section of a hybrid artificial blood vessel according to one embodiment of the present invention;

Fig.4 is a X-ray photoelectron micrograph showing the exterior surface of a hybrid artificial blood vessel comprising a biodegradable polymer-supporting layer according to one embodiment of the present invention;

Fig.5 is a scanning electron micrograph showing a section of an artificial blood vessel layer before adding a biodegradable polymer-supporting layer according to one embodiment of the present invention; and

Fig.6 is an X-ray photoelectron micrograph showing the exterior surface of an artificial blood vessel layer before adding a biodegradable polymer-supporting layer according to one embodiment of the present invention.

Detailed Description of the Invention

The present invention is directed to an artificial blood vessel to improve patency of the blood vessel, particularly regarding an artificial blood vessel of a hybrid type comprising biodegradable polymer-supporting layers. More specifically, the present invention is directed to a hybrid artificial blood vessel capable of forming vascular tissues on a non-degradable artificial blood vessel layer by reinforcing the non-degradable artificial blood vessel layer with a drug and with biodegradable polymer-supporting layers and then culturing blood vessel cells seeded on the vessel layer. Also, the present invention is directed to a manufacturing process of the hybrid artificial blood vessel.

The artificial blood vessel of the present invention is a hybrid type wherein the biodegradable polymer-supporting layers are formed on at least one side of the inside and outside of the non-degradable artificial blood vessel layer. The biodegradable polymer-supporting layers formed on at

least one side of the inside and outside of the non-degradable artificial blood vessel layer may include a drug and cause biodegradation so that the blood vessel cells can be regenerated as a patient's own blood vessel tissue.

Thus, the surface of the hybrid artificial blood vessel of the present invention in this manner substitutes the biodegradable polymer-supporting layers formed on the inside and/or outside of the vessel layer for a non-degradable artificial blood vessel layer having low cell adhesivity, resulting in improving the cell adhesivity of the artificial blood vessel. Since the cells adhered on the inside and/or outside of the biodegradable polymer-supporting layer are cultured and then regenerated as a recipient's own blood vessel tissues during the biodegradation of the polymer-supporting layer, the artificial blood vessels for tissue engineering use may be produced by inducing histogenesis on the inside and/or outside of the hybrid artificial blood vessel.

The drug is also contained in the pores of the non-degradable artificial blood vessel layer and in the

biodegradable polymer-supporting layer thereon to form a biodegradable polymer-supporting layer containing the drug, whereby a hybrid artificial blood vessel containing the drug is produced. The hybrid artificial blood vessel can be varied by controlling the kind of add-on drug, the release rate of the drug, the degradation rate of biodegradable polymer-supporting layers, cell adhesivity, and the thickness of the generated tissue formed from the degradation of the supporting layer. Thus, the hybrid artificial blood vessel of the present invention can be used in a great range of application via biodegradation and local drug transmission.

In the hybrid artificial blood vessel of the present invention, materials for the biodegradable polymer-supporting layer formed on the non-degradable artificial blood vessel layer may comprise at least one polymer selected from the group consisting of synthetic polymers, such as polyglicolide, polylactide, poly(lactic-co-glicolic acid) and polycaprolactone, or natural polymers, such as chitosan, gelatin, alginic acid, hyaluronic acid and

collagen. The material is preferably porous.

For the hybrid artificial blood vessel of the present invention, the non-degradable artificial blood vessel layer comprises preferably polyurethane derivatives, DacronR or drawn polytetrafluoroethylene(ePTFE). More preferably, it is ePTFE.

As described above, the hybrid artificial blood vessel of the present invention may further comprise a drug which may be stored in at least one region selected from the group consisting of the microporous space of the non-degradable artificial blood vessel layer, the biodegradable polymer-supporting layers, and the interfaces of the artificial blood vessel layer and the supporting layers. Examples of such a drug comprise at least one drug selected from the group consisting of a drug promoting tissue generation and cell growth by acting a signal on cell culture, such as vascular endothelial growth factor, fibroblast growth factor, nerve growth factor, platelet-derived growth factor and so forth; a drug acting as a signal controlling the interaction with blood or blood cell such as heparin,

thrombin, and so forth; and a drug improving cell adhesion such as laminin, fibronectin, collagen and so forth.

Preferably, the biodegradable polymer-supporting layer is repetitively coated on the artificial blood vessel layer.

Furthermore, the surface of the non-degradable artificial blood vessel layer is preferably modified physically or chemically.

The above-mentioned hybrid artificial blood vessel of the present invention is obtained by dissolving biodegradable polymer in organic solvents to prepare biodegradable polymer solution A; adding porogen to the polymer solution A; dissolving the same or different biodegradable polymer with the above biodegradable polymer in organic solution to prepare biodegradable polymer solution B; incorporating the biodegradable polymer solution B into the micropore of artificial blood vessel layers; inserting tubes to the inside and outside of the artificial blood vessel layers; filling the biodegradable polymer solution A in the space between the artificial blood vessel layer and the tubes; drying the artificial blood vessel to

remove the organic solvent; and incubating the artificial blood vessel in a water bath to remove the porogen.

The biodegradable polymer may contain a drug in advance.

Preferably, the porogen may comprise ammonium bicarbonate or sodium chloride.

The organic solvents for dissolving the biodegradable polymer may use any solvents conventionally available for dissolving the polymer and is not limited in this regard. Preferably, dichloromethane or dioxane can be used.

The biodegradable polymer is possible to use a biodegradable polymer bead containing a drug.

For example, a method of incorporating the biodegradable polymer solution B into the micropore of the non-degradable artificial blood vessel layer comprises blocking the alternative terminal of the non-degradable artificial blood vessel layer with tourniquets, placing the biodegradable polymer solution B with/without a drug in a syringe, and filtering the solution B into the artificial blood vessel layer so that the biodegradable polymer can be

incorporated into the micropore of the artificial blood vessel wall.

To fill the biodegradable polymer solution A into the space formed between the artificial blood vessel layer and the tubes, the alternative terminals of the non-degradable artificial blood vessel layer and of the tubes inserted into the inside and outside of the artificial blood vessel layer are aligned, the aligned terminals of the tubes and the artificial blood vessel layer are enclosed with Teflon film and tape to form a configuration in which the alternative terminals of two tubes and of the blood vessel layer are blocked while having the same axis, and then the aligned configuration upends to place the blocked terminals in the bottom, followed by filling the biodegradable polymer solution A into the empty space in the inside and outside of the artificial blood vessel layer.

According to such a method, the hybrid artificial blood vessel which the biodegradable polymer-supporting layers with and/or without a drug are formed on the surfaces inside

and outside the non-degradable artificial blood vessel layer and in the micropore of the blood vessel wall can be produced.

Examples

The present invention as described above will be further exemplified by the following specific examples and experimental examples which are provided by way of illustration and not for limitation thereof.

Example 1: Preparation of PLGA/chitosan/ePTFE hybrid artificial blood vessel

0.6g of PLGA[Poly(Lactic-co-Glycolic Acid): 75:25] was added to a vial for 20 ml containing 6 ml of dioxane and dissolved for 3 hours at an ambient temperature with stirring, then 6 g of ammonium bicarbonate was added to the solution. Similarly, chitosan was added to a vial for 20 ml containing 0.2M of acetic acid solution to produce 1% of a chitosan solution.

The 1% of chitosan solution was filtered through ePTFE artificial blood vessel having 6 mm of inner diameter in order to load the solution in the micropore of ePTFE wall. As shown in Fig. 2, the ePTFE artificial blood vessel containing chitosan solution was arranged with two plastic tubes having different diameters (one tube having 4 mm of outer diameter and another tube having 10 mm of inner diameter) on the same axis in order to make a mould.

The PLGA solution was added to the space between the plastic tube having 4 mm of outer diameter and the inside of ePTFE artificial blood vessel and between the outside of ePTFE artificial blood vessel and the plastic tube having 10 mm of inner diameter in order to make a mould containing the biodegradable polymer. After drying the formed mould, porogen in the mould made of the plastic tubes was removed to produce a hybrid artificial blood vessel which biodegradable supports having pore therein are formed on the inside and outside of ePTFE artificial blood vessel.

Example 2: Preparation of PLGA/gelatin/ePTFE hybrid

artificial blood vessel

A hybrid ePTFE artificial blood vessel was prepared as in example 1 except gelatin was substituted for chitosan.

Example 3: Preparation of PLGA/hyaluronic acid/ePTFE hybrid artificial blood vessel

A hybrid ePTFE artificial blood vessel was prepared as in example 1 except hyaluronic acid was substituted for chitosan.

Example 4: Preparation of a hybrid artificial blood vessel using sodium chloride as a porogen

A hybrid ePTFE artificial blood vessel was prepared as in example 1 except sodium chloride was substituted for ammonium bicarbonate.

Example 5: Preparation of a hybrid artificial blood vessel using a biodegradable support supplemented with biodegradable beads containing a drug

A hybrid ePTFE artificial blood vessel was prepared as

in example 1 except biodegradable beads containing a drug were substituted for PLGA solution.

Example 6

A hybrid ePTFE artificial blood vessel was prepared as in example 1 except chemically modified ePTFE was substituted for ePTFE.

Experimental Example 1

Determination of morphological changes of a hybrid ePTFE artificial blood vessel

Using scanning electron microscopy, the morphological changes after a hybrid ePTFE artificial blood vessel was supplemented with biodegradable supports were determined. Fig. 5 is a scanning electron micrograph showing a section of an ePTFE artificial blood vessel before adding biodegradable polymer supports. Fig. 3 is a scanning electron micrograph showing a section of an ePTFE artificial blood vessel supplemented with biodegradable polymer supports according to example 1. As shown in Figs. 3 and 5,

it was confirmed that only ePTFE was existed before the preparation of the support, but the porous, biodegradable support was supplemented in the inside and outside of ETPFE artificial blood vessel after the preparation of the support. It was also recognized that the supports were supplemented on the outside surface of ePTFE artificial blood vessel and were porous.

Experimental example 2

Determination of the ability of biodegradation resulting from a hybrid ePTFE artificial blood vessel

To examine the degradation phenomenon of the biodegradable support present in a hybrid artificial blood vessel, the prepared hybrid artificial vessel was dipped in a buffer solution (pH 7.0) at an ambient temperature and observed for the degradation phenomenon over 1 month. Sample which suffered from the degradation by hydration was dried in a desiccator and the weight changes of dried sample were determined every a interval. Similarly, the dried weight of another sample was determined as in the above manner except

the sample was dipped in a weak acid solution. From the result, it was confirmed that the weight of the samples was gradually reduced due to the formation of the artificial blood vessel supplemented with the biodegradable supports.

Experimental example 3

Chemical composition of ePTFE artificial blood vessel supplemented with biodegradable supports

The changes of chemical composition in the surface of a hybrid ePTFE artificial blood vessel were analyzed by X-ray photoelectron microscopy after adding biodegradable supports. From the X-ray photoelectron microscopies for the surface of ePTFE artificial blood vessel shown in the Figs.4 and 6, it was found that the surface was comprised of fluorine and carbon only. However, no fluorine was detected from ePTFE artificial blood vessel supplemented with the supports although fluorine is a chemical component of ePTFE. It was confirmed that the ePTFE artificial blood vessel supplemented with the supports was comprised only of carbon and oxygen, which are the chemical components of PLGA. From

the result, it was demonstrated that a hybrid artificial blood vessel supplemented with biodegradable supports had been formed.

Experimental example 4

Culturing experiment of fibroblast on the surface of a hybrid artificial blood vessel

To confirm the biocompatibility of the ePTFE artificial blood vessel after modifying the surface of the vessel, fibroblast was cultured on the ePTFE artificial blood vessel before modifying the surface of the vessel and that after modifying the surface of the vessel for comparison. In the ePTFE artificial blood vessel before modifying the surface and a sample supplemented with the supports according to the method of example 1, it was shown that cell adhesivity was significantly increased. Also, on the sample before modifying the surface of the vessel and on the sample after modifying the surface of the vessel, fibroblast (1x106 cell/cm2) was directly cultured independently or fibroblast (1x106 cell/cm2) was independently cultured after adsorbing

cell adhesion protein such as fibronectin. In the case of ePTFE artificial blood vessel, the inductive phenomenon of cell adhesion was observed on up to 5% of the surface area of vessel. However, in the ePTFE artificial blood vessel supplemented with biodegradable supports according to the method of example 1, it was confirmed that cell adhesivity had been significantly increased and induced over 80% of the surface area of the blood vessel.

Experimental example 5

Determination of drug transmission from a hybrid ePTFE artificial blood vessel containing a drug

The drug release property of a hybrid ePTFE artificial blood vessel was examined using Tritium-linked H3-Heparin. From the result, it was confirmed that the drug had been slowly released from the micropore of the ETPFE artificial blood vessel.

As described in above, the present invention provides a hybrid artificial blood vessel and a manufacturing process

of the same which represents the improved patency of an artificial blood vessel due to the generation of new vascular tissues. The hybrid artificial blood vessel of the present invention allows degrading the biodegradable polymer supports with the passage of time while generating new vascular tissues.

Industrial Applicability

Although a preferred embodiment of the present invention has been described for illustrative purposes, those skilled in the art will appreciate that various modifications, additions and substitutions are possible, without departing from the scope and spirit of the invention as disclosed in the accompanying claims.

What is claimed is:

1. A hybrid artificial blood vessel comprising a biodegradable polymer-supporting layer on at least one of an inside and an outside of a non-degradable artificial blood vessel layer.

2. The hybrid artificial blood vessel as claimed in claim 1, wherein the biodegradable polymer comprises at least one polymer selected from the group consisting of synthetic polymers such as polyglicolide, polylactide, poly(lactic-co-glicolic acid) and polycaprolactone, or natural polymers such as chitosan, gelatin, alginic acid, hyaluronic acid and collagen.

3. The hybrid artificial blood vessel as claimed in claim 1, wherein the non-degradable artificial blood vessel layer comprises polyurethane derivatives, DacronR or drawn polytetrafluoroethylene.

4. The hybrid artificial blood vessel as claimed in claim 1, further comprising a drug, which is stored in at least one region selected from the group consisting of the microporous space of the non-degradable artificial blood vessel layer, the biodegradable polymer-supporting layer, and the interface of the artificial blood vessel layer and the supporting layer.

5. The hybrid artificial blood vessel as claimed in claim 4, wherein the drug comprises at least one selected from the group consisting of vascular endothelial growth factor, fibroblast growth factor, nerve growth factor, platelet-derived growth factor, heparin, thrombin, laminin, fibronectin and collagen.

6. The hybrid artificial blood vessel as claimed in claim 1, wherein the biodegradable polymer-supporting layer is porous.

7. The hybrid artificial blood vessel as claimed in

claim 1, wherein the biodegradable polymer-supporting layer is repetitively coated on the artificial blood vessel layer.

8. The hybrid artificial blood vessel as claimed in claim 1, wherein the surface of the non-degradable artificial blood vessel layer is modified physically or chemically.

9. A manufacturing process of a hybrid artificial blood vessel, comprising the steps of:

dissolving biodegradable polymer in organic solvent to prepare biodegradable polymer solution A;

adding porogen to the polymer solution A;

dissolving the same or different biodegradable polymer with the above biodegradable polymer in organic solvent to prepare biodegradable polymer solution B;

incorporating the biodegradable polymer solution B into micropores of an artificial blood vessel layer;

inserting tubes to the inside and outside of the artificial blood vessel layer;

filling the biodegradable polymer solution A in a space between the artificial blood vessel layer and the tubes;

drying the artificial blood vessel layer filled with the biodegradable polymer solution A to remove the organic solvent; and

incubating the artificial blood vessel layer filled with the biodegradable polymer solution A in a water bath to remove the porogen.

10. The manufacturing process as claimed in claim 9, wherein the biodegradable polymer comprises at least one polymer selected from the group consisting of polyglicolide, polylactide, poly(lactic-co-glicolic acid), chitosan, gelatin, alginic acid and collagen.

11. The manufacturing process as claimed in claim 9, wherein the non-degradable artificial blood vessel layer comprises polyurethane derivatives, DacronR or drawn polytetrafluoroethylene.

12. The manufacturing process as claimed in claim 9, wherein the biodegradable polymer solutions A and B further comprise a drug which contains growth factors or extracellular matrices.

13. The manufacturing process as claimed in claim 12, wherein the drug comprises at least a drug selected from the group consisting of vascular endothelial growth factor, fibroblast growth factor, nerve growth factor, platelet-derived growth factor, heparin, thrombin, laminin, fibronectin and collagen.

14. The manufacturing process as claimed in claim 9, wherein the surface of the non-degradable artificial blood vessel layer is modified physically or chemically.

15. An artificial organ for tissue engineering use prepared by any one of manufacturing processes of claims 9 and 14.

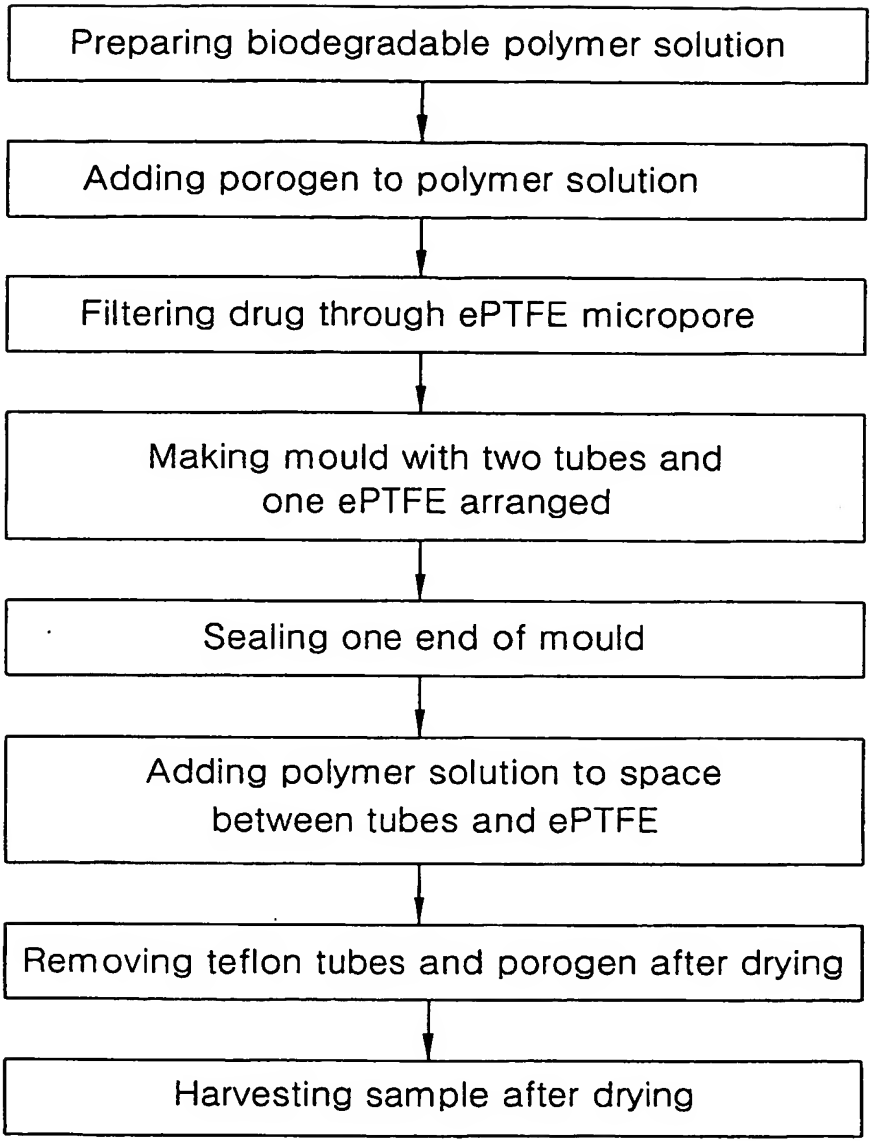

Preparing biodegradable polymer solution
Adding porogen to polymer solution
Filtering drug through ePTFE micropore
Making mould with two tubes and one ePTFE arranged
Sealing one end of mould
Adding polymer solution to space between tubes and ePTFE
Removing teflon tubes and porogen after drying
Harvesting sample after drying

FIG. 1

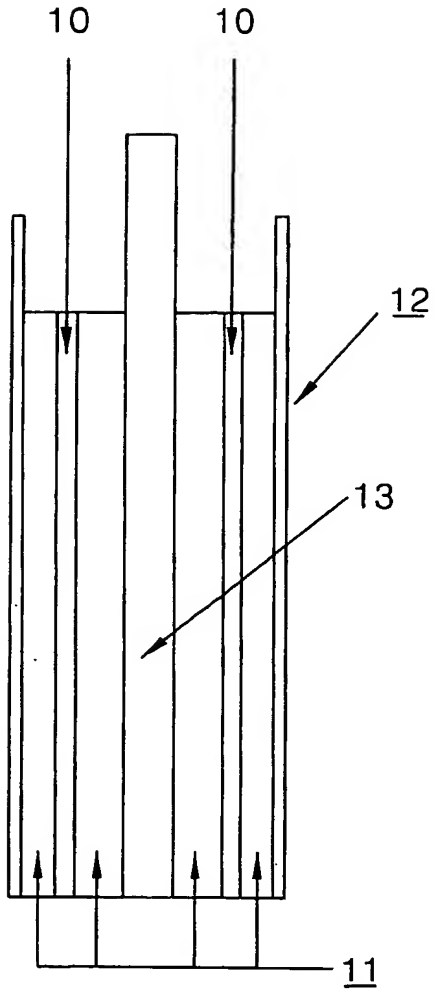


FIG.2

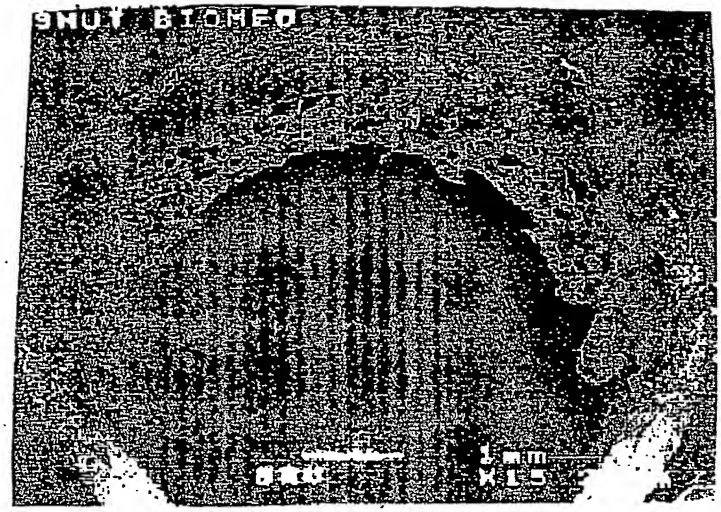


FIG.3

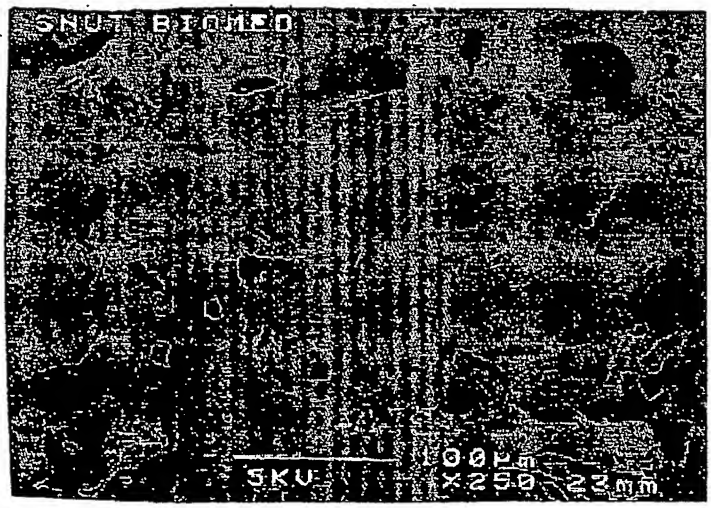


FIG.4

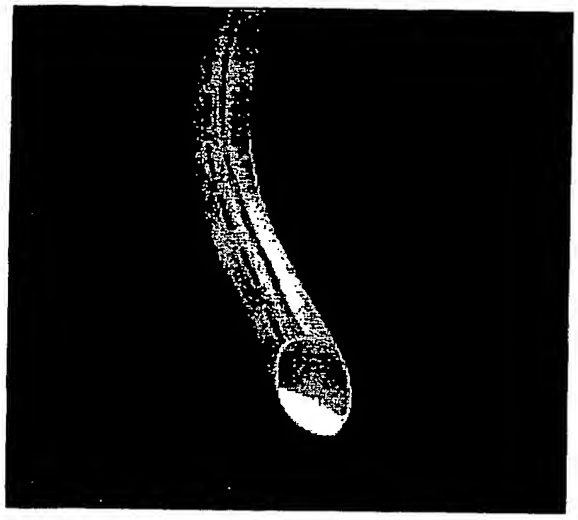


FIG.5

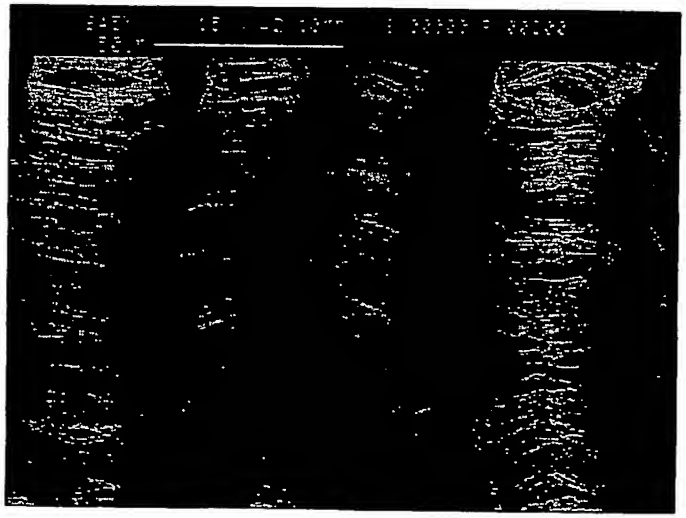


FIG. 6

INTERNATIONAL SEARCH REPORT

...ternational application No.
PCT/KR03/00611

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 A61L 27/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61L 27/34, A61F 2/00, A61L27/00, A61F2/06

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korea Patent and Applications for Inventions since 1975
Korea Utility Models and Applications for Utility Models since 1975
Japanese Utility Models and application for Utility Models since 1975

Electronic data base consulted during the internatnional search (name of data base and, where practicable, search terms used)
eKIPASS, WPI, USPTO, INSPECT"blood, vessel, prosthesis, ePTFE, poly glycolic acid, biodegradable, etc."

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6334872 B1 (Organogenesis Inc.) 01 Jan 2002 -see Figure1B and pages 2-10	1-8
Y	US 5449382 A (Michael P. Dayton) 12 Sep 1995 -see pages 3-5	1-8
Y	US 4416028 A (Ingvar Eriksson et al.) 22 Nov 1983 -see the entire document-	1-3, 6-8
A	US 6197051 B1 (Boston Scientific Corporation), 06 Mar 2001 -see claims-	1-8

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 JULY 2003 (07.07.2003)	08 JULY 2003 (08.07.2003)

Name and mailing address of the ISA/KR	Authorized officer
Korean Intellectual Property Office 920 Dunsan-dong, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140	JOO, Young Sik Telephone No. 82-42-481-5995

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR03/00611

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6334872 B1	01 Jan 2002	WO 95/22301 A1	24 Aug 1995
		EP 746268 A4	01 Apr 1998
		CA 2183056 C	10 Jul 2001
		JP 9509085 T2	16 Sep 1997
US 5449382 A	12 Sep 1995	none	
US 4416028 A	22 Nov 1983	none	
US 6197051 B1	06 Mar 2001	WO 98/57671 A3	15 Apr 1999
		EP 1011739 A2	28 Jun 2000
		JP 12513988 T2	24 Oct 2000